Clinical question.

Primary Question:
In adult cardiac arrest (pre-hospital or in-hospital) due to benzodiazepine toxicity (P), does the use of flumazenil (I), as opposed to standard care (according to treatment algorithm) (C) improve outcome (O) (e.g., ROSC, survival)?

Secondary Questions:
In adults with severe cardiovascular toxicity or life-threatening toxicity (pre-hospital or in-hospital) due to benzodiazepine (P), does use of flumazenil (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (e.g., neurologically-intact survival)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/therapy

State if this is a proposed new topic or revision of existing worksheet: New

Conflict of interest specific to this question
Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).


EMBASE: Search for “Benzodiazepine or Diazepam or Lorazepam or Oxazepam or Alprazolam or Clonazepam or Midazolam or Temazepam” and “Flumazenil” and “Heart Arrest OR Cardiopulmonary Resuscitation” for articles published 1950–2009 in all fields then combine the result.

Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials: Search for all terms independently and combined.

AHA EndNote Master Library: Search for “Benzodiazepine or Diazepam or Lorazepam or Oxazepam or Alprazolam or Clonazepam or Midazolam or Temazepam” and “Flumazenil” and “Heart Arrest OR Cardiopulmonary Resuscitation”

Review of references of articles (or reviews) of relevance

• State inclusion and exclusion criteria
  - Primary Question:
    Study included if: Cardiac arrest was reported secondary to benzodiazepine toxicity. Articles published 1950–2009.
    Study excluded if: No cardiac arrest or cardiac arrest was not secondary to benzodiazepine toxicity. Pediatric studies, and abstract only studies.
  - Secondary Questions:
    Study included if: Cardiovascular toxicities were reported secondary to benzodiazepines. Articles published 1950–2009.
    Study excluded if: No cardiovascular toxicity or cardiovascular toxicities were not related to benzodiazepines. Pediatric studies, and abstract only studies.

• Number of articles/sources meeting criteria for further review:
  Primary Question:
  Seven studies met criteria for further review. Of these 5 were LOE 4 (one retrospective chart review without control, 3 case reports, and one review article), and 2 LOE 5 (2 animal studies).
  Secondary Questions:
  Seven studies met criteria for further review. Of these, one LOE 1 (RCT), 5 LOE 4 (3 case reports, 2 prospective cohort), and one LOE 5 (animal study) were included.
## Summary of evidence

### Evidence Supporting Clinical Question

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<th>Level of evidence</th>
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<td>Mullins, 1999 CE*</td>
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* = non-arrest toxicity

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*italics* = Animal studies
### Evidence Neutral to Clinical question

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<td>Arepally, 2001 B* Geller, 1991 B*</td>
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A = Return of spontaneous circulation  
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### Evidence Opposing Clinical Question

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A = Return of spontaneous circulation  
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E = Other endpoint  
* = non-arrest toxicity  
Italics = Animal studies
Reviews Final Comments and Assessment of Benefit / Risk:

Primary Question:

- Our search did not identify any human studies or reports of any patients who had cardiac arrest solely resulting from benzodiazepine toxicity alone that had improved outcomes from either standard care or flumazenil.
- Our search identified reports of cardiac arrests resulting after exposure to combinations of medication that included one of the benzodiazepines [Beauvoir, 1991, 154; Gillart, 2008, 510; Nordt, 1997, 357; Lheureux, 1992, 184; Machin, 1998, 598].
- One animal model showed that benzodiazepines in combination with other hypnotics can result in cardiac arrest in ducks, and with other resuscitation efforts and modality of treatment, flumazenil may play a role in ROSC; but no control group to prove that the flumazenil can be used alone to achieve ROSC was used [Machin, 1998, 598].
- Our search identified one retrospective chart review of 5439 patients exposed to one benzodiazepine (midazolam) and only 30% of them received > 5 mg. Of these only 3 patients (0.099%) had respiratory depression that was associated with opioid co-ingestion, were elderly, and used high-dose midazolam. None of the patients developed cardiac arrest [Classen, 1992, 213].
- We identified 3 case reports of 3 patients who had cardiac arrest resulting after overdose on benzodiazepines with other medication (calcium-channel blockers, tricyclic antidepressants, ethanol, zopiclone), which are most likely the cause of the arrest, either alone or in combination, than the benzodiazepines alone. None of these patients were treated with flumazenil during the resuscitation phase [Beauvoir, 1991, 154; Gillart, 2008, 510; Marrache, 2004, 503]. Standard therapy in these cases led to ROSC, and 2 patients survived to hospital discharge [Beauvoir, 1991, 154; Gillart, 2008, 510]. In one case report the patient was discharged without neurological deficit [Gillart, 2008, 510]. One patient had ROSC but was brain dead, and he was treated with flumazenil later to reverse the neurological effects but without response [Marrache, 2004, 503].
- One review article reported that benzodiazepines can cause cardiac arrest, but it is most likely with other co-ingestions, particularly opioids. Although cardiac arrest can be attributed to respiratory depression rather than direct cardiotoxicity, respiratory depression may not respond to flumazenil alone [Nordt, 1997, 357].
- In one animal model RCT study, reversal of benzodiazepines sedation with flumazenil in dogs treated with both benzodiazepines and tricyclic antidepressant, resulted in worsening in the TCA cardiotoxicity and the death of 2 dogs as opposed to the dogs that did not receive flumazenil. This can be attributed to a probable protective effect for the benzodiazepines against the cardiotoxicity of the TCAs rather than direct cardiotoxicity of either flumazenil or benzodiazepines [Lheureux, 1992, 184].

The primary question could not be answered since there is no report of cardiac arrest from benzodiazepines alone and there was no cardiac arrest patient that was resuscitated with flumazenil alone. Patients who had cardiac arrest and overdosed on benzodiazepines in combination with other medication with known cardiotoxic effects were resuscitated successfully without flumazenil, and the standard therapy was assumed but not reported to be the modality of therapy.

Secondary Question:

- No human studies or reports of any patients who had severe cardiac toxicity solely resulting from benzodiazepine toxicity alone that had improved outcomes from either standard care or flumazenil that our search could identify.
- Our search identified reports of cardiac toxicity resulting after exposure to combinations of medication that include one of the benzodiazepines [Arepally, 2001, 185].
- Animal and human studies have shown that benzodiazepines may cause minimal change in hemodynamic parameters but not severe enough to cause life-threatening changes, particularly if used alone [Geller, 1991, 207; Spivey, 1993, 1813; 184; Hara, 2001, 135]. If used in combination with other known cardiovascular toxic medication, particularly opioids or tricyclic antidepressants, severe hemodynamic effects were reported. Standard care directed mainly toward the other co-ingestion effects was the reported effective therapy [Lheureux, 1992, 184].

1) The following are reports of a possible direct effect of benzodiazepines on the human cardiovascular system:

a. Required resuscitation with standard care:
   - One case report of anaphylactoid reaction to midazolam. The patient was treated with standard therapy alone. Flumazenil was not reported as part of the resuscitation [Fujita, 1994, 811].

b. Reversal of cardiac toxicity with flumazenil:
   - One case report of a patient overdosed on benzodiazepine (alprazolam), which resulted in a marked first-degree atrioventricular block that was reversed twice by flumazenil. This is the only case report that showed that flumazenil might have a reversal effect on the heart from benzodiazepine toxicity. The author of this report proposed that
benzodiazepines act peripherally at the same site as the calcium-channel blockers rather than at a separate benzodiazepine receptor, which explains the observed conduction defect. Flumazenil may have some adjunctive role in the future management of cardiac conduction delays resulting from calcium-channel blocker toxicity [Mullins, 1999, 367].

c. Did not require resuscitation:
- Case report of 3 patients who developed bigeminy, trigeminy, and tachycardia after premedication with intramuscular midazolam for general anesthesia. None of these patients developed severe hemodynamic instability to require resuscitation and none of them received flumazenil [Arcos, 1987, 612].
- One prospective cohort study of 594 patients showed that the use of a combination of midazolam and fentanyl for conscious sedation can result in hypotension that did not require resuscitation or use of flumazenil to reverse the hypotension effect. In this cohort standard care was adequate for reversal of the hypotension resulting from this combination therapy [Arepally, 2001, 185].
- One prospective cohort study of 5 patients showed that diazepam in therapeutic doses caused a slight decrease in mean arterial pressure MAP, which was not clinically significant. Flumazenil reversed the sedation effect of the BZD but not the hemodynamic changes. This study showed that BZD might have hemodynamic changes that might be more pronounced in overdose, but flumazenil will not reverse this effect. This can be attributed to different mechanisms for hypotension not related to the flumazenil site of action [Geller, 1991, 207].
- In one RCT study of 170 benzodiazepine-overdosed patients, flumazenil rapidly and effectively reversed the CNS depression associated with BZD. Pulse rate and blood pressure showed no statistically or clinically significant change for patients who received flumazenil or placebo. No cardiovascular toxicities were reported in this clinical trial prior to the treatment. Two (6.1%) flumazenil-treated patients developed hypotension after receiving flumazenil. This was reported as clinically nonsignificant [Spivey, 1993, 1813].

2) In one animal model of guinea pig heart, diazepam produced negative inotropic effect on the guinea pig heart, and the mechanism of action is independent of the BZD receptor. Flumazenil did not reverse this negative inotropic effect [Hara, 2001, 135].

Summary:
- One animal model.
- 774 human benzodiazepines exposures:
  - One severe reaction (anaphylactoid) to benzodiazepines treated with standard care with improved outcome
  - One non-clinically significant cardiovascular toxicity treated with flumazenil with improved outcome
  - 772 non-clinically significant cardiovascular toxicities that did not require resuscitation or flumazenil reversal.

Acknowledgements:

Citation List

  - LOE: 4
  - Quality: poor
  - Neutral
  Comment: Three episodes of ventricular bigeminy and trigeminy and of ventricular tachycardia after premeditation following an intramuscular injection of midazolam were reported. All these dysrhythmias were self-limited and resolved within 2–4 h of midazolam administration.

  - LOE: 4
  - Quality: fair
  - Neutral
Comment: The two medications used in all procedures were midazolam and fentanyl. For all procedures, respiratory adverse events were the most frequent (4.7%), while the incidence of sedative and major adverse events was 4.2% and 2.0%, respectively. All major adverse events were episodes of hypotension (< 80 mm Hg systolic). None of the patients required intubation. There were no cardiac arrests related to conscious sedation. There was a general trend toward increased adverse events with increases in the received dose of midazolam and fentanyl, but this did not reach statistical significance. Flumazenil was given to reverse the sedation. There was no report of the use of flumazenil to reverse the hypotension. The hypotension is most likely the effect of the combination of the drugs or fentanyl alone rather than midazolam alone.


- LOE: 4
- Quality: poor
- Neutral

Comment: Patient overdosed on a massive dose of both calcium-channel blockers and benzodiazepine. The cardiac arrest most likely resulted from CCB, but assuming the BZD played a role, the patient had ROSC and survived to home discharge. There was no report that flumazenil was used in the resuscitation process.


- LOE: 4
- Quality: poor
- Neutral

Comment: Three patients (0.099%) experienced respiratory arrest, no cardiac arrest from midazolam. Respiratory arrest was associated with high doses of midazolam, concurrent use of opiates, and use in elderly patients. All patients survived.


No abstract available.

- LOE: 4
- Quality: poor
- Neutral

Comment: A case was reported of an anaphylactoid reaction to midazolam in a patient undergoing an anterior cervical spine fusion. When 10 mg midazolam was injected IV near the end of surgery, taking about 2.5 h to facilitate mechanical ventilation postoperatively, the patient suddenly developed severe hypotension to 57 mm Hg systolic blood pressure and tachycardia of 135 bpm. A widespread flush on the body and neck was observed. The patient was treated with standard therapy alone. Flumazenil was not reported as part of the resuscitation.


- LOE: 4
- Quality: fair
- Neutral

Comment: Diazepam in therapeutic doses causes a slight decrease in MAP, which was not clinically significant. Flumazenil reverse the sedation effect of the BZD but not the hemodynamic changes. This study showed that BZD might have hemodynamic changes that might be more pronounced in overdose, but flumazenil will not reverse this effect. This can be attributed to different mechanisms for hypotension not related to the flumazenil site of action.


- LOE: 4
Comment: Patient co-ingested TCA, which could be the reason for the cardiac arrest. Patient was resuscitated pre-hospital, but no flumazenil was reported. There are reports of bad outcomes, particularly seizures, after reversal of BZD with flumazenil in patients who co-ingested TCA. Patients survived to hospital discharge without neurological deficit. Hypothermia may play a rule in this good outcome.


Comment: Diazepam produces a negative inotropic effect on guinea pig heart, and the mechanism of action is independent of the BZD receptor. Flumazenil did not reverse this negative inotropic effect.


Comment: The BZDs do not have direct cardiovascular effect, while TCAs do. The dogs that received BZD + TCA or BZD alone did not have cardiotoxicity. Dogs that received BZD + TCA then reversed with flumazenil showed worsening of TCA cardiotoxicity. Two dogs died. There is probably a cardiac protective effect of BZD against TCA cardiotoxicity, and reversal of this effect with flumazenil led to the dysrhythmias and death.


Comment: All ducks received medetomidine–midazolam–ketamine in combination, including the one duck that died and the 3 that required resuscitation. Reversal was achieved with both atipamezole and flumazenil at the same time. Although, midazolam was one of the 3 components that resulted in the arrest, other components or the added effects of the 3 may result in the arrest. In addition to resuscitation, flumazenil in combination with atipamazole was used in the reversal of the effect. The flumazenil effect by itself or in combination with atipamazole cannot be attributed to the successful ROSC since there was no control for this effect, including standard of care.

This is animal study, and the only study that showed that any benzodiazepine can cause cardiac arrest or can be reversed and resuscitated with flumazenil. The existence of other combination in both the causation for cardiac arrest and the treatment make this study less likely to answer the primary question in adults human.


Comment: Patient overdosed on 3 substances, one of them was a benzodiazepine and the other (zopiclone) was a non-BZD benzodiazepine-like medication. Resuscitation for the cardiac arrest did not include flumazenil, which led to ROSC but with brain death. The blood bromazepam level was high, and cardiac arrest could be attributed to the co-ingestion of the 3 substances together. Flumazenil was used later to reverse the neurological effect, but this was not effective.
- LOE: 4
- Quality: good
- Supportive

Comment: Case report of alprazolam overdose associated with marked first-degree atrioventricular block reversed by flumazenil. The PR shortened from 500 ms to 216 ms after first dose of flumazenil. Forty minutes later the patient became obtunded and the PR interval increased to 527 ms, which decreased to 184 ms after the second flumazenil dose. The PR interval was normal before and after that visit (180 and 184 ms, respectively). The author proposed that benzodiazepines might have calcium-channel blocking properties, which explains the observed conduction defect.

- LOE: 4
- Quality: poor
- Neutral

Comment: Midazolam has been associated with respiratory depression and cardiac arrest when used in combination with an opioid, particularly in the elderly. No report of usefulness of flumazenil in reversal of these cardiac arrests or use of flumazenil in the resuscitation of the patient who had cardiac arrest.

- LOE: 1
- Quality: fair
- Neutral

Comment: Flumazenil rapidly and effectively reverses the CNS depression associated with BZD. Pulse rate and blood pressure showed no statistically or clinically significant change for patients who received flumazenil or placebo. No cardiovascular toxicities were reported in this clinical trial prior to the treatment. Two (6.1%) flumazenil-treated patients developed hypotension after receiving flumazenil. These were reported as clinically nonsignificant.

- LOE: 1
- Quality: fair
- Opposing

Comment: In this trial significant adverse reaction were reported in 1.85% of patients receiving flumazenil; 3 subjects had seizures and 1 that seized had ventricular tachycardia temporally related to flumazenil administration. In 2 of the 3 patients with significant adverse reactions co-ingestion of tricyclic antidepressants had occurred.